Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

for

Angew. Chem. Int. Ed. Z53716

69451 Weinheim, Germany

Enantioselective Organocatalytic Direct Aldol Reactions of α-Oxyaldehydes: Step One in a Two Step Synthesis of Carbohydrates

Alan B. Northrup, Ian K. Mangion, Frank Hettche and David W. C. MacMillan*

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[2] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by anisaldehyde stain.

^{1}H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility or from the UC Irvine Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex Γ-DM (30 m x 0.25 mm) column or an ASTEC Chiraldex Γ-BP (30 m x 0.25 mm) as noted. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a Chiralcel AD column (25 cm) and AD guard (5 cm), a Chiralcel OJ column (25 cm) and OJ guard (5 cm) or a Chiralcel ODH column (25 cm) and ODH guard (5 cm) as noted.

(2*S*, 3*S*)-3-Hydroxy-2,3-bis-(benzylyloxy)-propionaldehyde (Table 1, entry 2). A suspension of benzyloxyacetaldehyde (1.0 g, 6.66 mmol) and L-proline (38.3 mg, 0.33 mmol) in dimethylformamide (13.3 mL) was stirred for 42 h at room temperature. The resulting solution was diltued with water (25 mL) and the organics extracted with ethyl acetate (3 x 25 mL). The resulting organics were then washed with brine and then) dried (Na_2SO_4). The organics were then concentrated and the resulting residue was purified by silica gel chromatography (1:19 ether: dichloromethane) to afford the title compound as a clear, colorless oil in 52% yield (518 mg, 0.31 mmol), 98% ee (*anti*), and as a 4:1 *anti*:*syn* mixture of diastereomers. Recovered starting material (442 mg) was resubjected to the above conditions to afford and additional 21% yield (210 mg) for a combined yield of 73%. IR (film) 3438, 3064, 3031, 2868, 1957, 1879, 1813, 1732, 1497, 1454, 1094, 738.9, 698.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): □9.72 (d, 1H, *J* = 1.8 Hz, CHO); 7.33 (m, 10H, Ar-H); 4.73 (d, 1H, *J* = 12.3 Hz, CH_2Ar); 4.56 (d, 1H, *J* = 12.3 Hz, CH_2Ar); 4.54 (d, 1H, *J* = 12.0 Hz, CH_2Ar); 4.49 (d, 1H, *J* = 12.0 Hz, CH_2Ar); 4.14 (m, 1H, C**H**OH); 3.93 (dd, 1H, *J* = 5.7, 1.8 Hz, C**H**CHO); 3.62 (m, 2H, CH_2OBn); 2.39 (d, 1H, *J* = 6.6 Hz, OH); ^{13}C NMR (75 MHz, $CDCl_3$): □202.1, 137.7, 137.1, 128.8, 128.7, 128.5, 128.4, 128.1, 128.0, 83.7, 73.7, 73.6, 71.1, 69.9; $[\alpha]_D$ = –30.6 (c = 0.47, $CHCl_3$); HRMS (CI) exact mass calcd for $[M+H]^+$ ($C_{19}H_{21}O_4$) requires *m*/*z* 301.1434, found *m*/*z* 301.1432. The enantiomeric purity was of the corresponding diol (after reduction of the title compound with $NaBH_4$) was determined by HPLC analysis using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min): (2*S*, 3*S*)-enantiomer: t_r = 23.7 min, (2*R*, 3*R*)-enantiomer: t_r = 32.3 min, *syn* isomers t_r = 27.2, 28.8 min. The diastereomer ratio was determined by ^1H NMR analysis of the crude title compound and verified by HPLC analysis after $NaBH_4$ reduction.

(2*S*, 3*S*)-3-Hydroxy-2,3-bis-(4-methoxybenzylyloxy)-propionaldehyde (Table 1, entry 3). A suspension of 4-methoxybenzyloxyacetaldehyde (180 mg, 1.0 mmol) and L-proline (5.8 mg, 0.05 mmol) in dimethylformamide (1.33 mL) was stirred for 48 h at room temperature. The resulting solution was then diltued with water (25 mL) and the organics extracted with ethyl acetate (3 x 25 mL). The resulting organics were then washed with brine and then dried (Na_2SO_4). The organics were then concentrated and the resulting residue was purified by silica gel chromatography (40% to 60% ethyl acetate: hexanes, linear gradient) afforded the title compound as a clear, colorless oil in 64% yield (116 mg, 0.32 mmol), 97% ee (*anti*), and as a 4:1 *anti*:*syn* mixture of

diastereomers along with 41 mg recovered starting material (83% yield based on recovered starting material). IR (film) 3445, 2915, 2838, 1723, 1613, 1514, 1250, 1174, 1098, 1033, 820.0, 516.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 9.67 (d, 1H, *J* = 1.5 Hz, CHO); 7.21 (m, 4H, Ar-H); 6.88 (m, 4H, Ar-H); 4.63 (d, 1H, *J* = 10.8 Hz, CH_2Ar); 4.48 (d, 1H, *J* = 11.4 Hz, CH_2Ar); 4.45 (d, 1H, *J* = 11.1 Hz, CH_2Ar); 4.41 (d, 1H, *J* = 11.4 Hz, CH_2Ar); 4.08 (m, 1H, C**H**OH); 3.88 (dd, 1H, *J* = 5.4, 2.1 Hz, C**H**CHO); 3.80 (s, 6H, OMe); 3.57 (m, 2H, CH_2OPMB); 2.47 (d, 1H, *J* = 6.6 Hz, OH); ^{13}C NMR (75 MHz, $CDCl_3$): 202.2, 159.5 (2), 132.1 (2), 130.1, 129.7, 114.2, 114.0, 83.3, 73.4, 73.2, 71.0, 69.5, 55.6 (2); $[]_D$ = –29.2 (c = 1.00, $CHCl_3$); HRMS (CI) exact mass calcd for $[M+NH_4]^+$ ($C_{20}H_{26}O_5N$) requires *m/z* 360.1811, found *m/z* 360.1827. The enantiomeric purity of the corresponding diol (after reduction of the title compound with $NaBH_4$) was determined by HPLC analysis using a Chiracel AD and AD guard column (15% ethanol/hexanes, 1 mL/min): (2*S*, 3*S*)-enantiomer: t_r = 25.9 min, (2*R*, 3*R*)-enantiomer: t_r = 35.5 min, *syn* isomers t_r = 29.6, 29.6 min. The diastereomer ratio was determined by ^1H NMR analysis of the crude title compound and verified by HPLC analysis after $NaBH_4$ reduction.

(2*S*, 3*S*)- 3-Hydroxy-2,4-bis-methoxymethoxy-butyraldehyde (Table 1, entry 4). A suspension of methoxymethoxyacetaldehyde (78 mg, 0.75 mmol) and L-proline (4.3 mg, 0.038 mmol) in dimethylformamide (0.75 mL) was stirred for 20 h at room temperature. The resulting solution was then diltued with water (25 mL) and the organics extracted with ether (3 x 25 mL). The resulting organics were then washed with brine and then dried (Na_2SO_4). The organics were then concentrated and the resulting residue was purified by silica gel chromatography (3:1 ether: pentane) to afford the title compound as a clear, colorless oil in 42% yield (33 mg, 0.16 mmol), 96% ee (*anti*), and as a 4:1 *anti*:*syn* mixture of diastereomers. IR (film) 3364, 2978, 2938, 1715.9, 1555, 1446, 1379, 1343, 1101, 1039, 837.9, 713.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 9.70 (d, 1H, *J* = 1.8 Hz, CHO); 4.81-4.61 (m, 4H, 2 CH_2OMe); 4.12 (m, 1H, C**H**OH); 4.04 (dd, 1H, *J* = 5.1, 1.2 Hz, C**H**CHO); 3.69 (m, 2H, CH_2OMOM); 3.38 (s, 6H, 2 OMe); 3.15 (d, 1H, *J* = 7.2 Hz, OH); ^{13}C NMR (75 MHz, $CDCl_3$): 200.9, 97.8, 97.3, 84.0, 71.0, 68.7, 56.6, 56.0; $[]_D$ = +2.4 (c = 1.00, $CHCl_3$); HRMS (CI) exact mass calcd for $[M+H]^+$ ($C_9H_{17}O_6$) requires *m/z* 209.1020, found *m/z* 209.1020. The enantiomeric purity of the corresponding acetonide (after reduction of the title compound with $NaBH_4$ and then acetonide formation with acetone) was determined using Chiracel GLC analysis using a Bodman Chiraldex -DM (30 m x 0.25 mm) column (120 ºC, 23 psi): (2*S*,

3*S*)-enantiomer: t_r = 26.7 min, (2*R*, 3*R*)-enantiomer: t_r = 25.7 min, *syn* isomers t_r = 29.7, 29.8 min. The diastereomer ratio was determined by ^{1}H NMR analysis of the crude title compound.

(2*S*, 3*S*)-3-Hydroxy-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-propionaldehyde (Table 1, entry 7). A suspension of (*tert*-butyl-dimethyl-silanoxy)-acetaldehyde (176 mg, 1.0 mmol) and L-proline (11.6 mg, 0.1 mmol) in 1,4-dioxane (2.0 mL) was stirred for 48 h at room temperature. The resulting solution was diluted with diethyl ether (20 mL), passed through a plug of silica gel and concentrated. Silica gel chromatography (15:1 pentane: diethyl ether) afforded the title compound as a clear, colorless oil in 62% yield (109 mg, 0.31 mmol), 88% ee (*anti*), and as a mixture of diatereomers (3:1 *anti*:*syn*). IR (film) 3455, 2956, 2930, 2897, 2886, 2859, 1736, 1473, 1362, 1256, 1117, 838, 780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): □9.63 (d, 1H, *J* = 1.6 Hz, CHO); 4.07 (dd, 1H, *J* = 5.5, 1.6 Hz, C**H**CHO); 3.95-3.84 (m, 1H, C**H**OH); 3.80-3.55 (m, 2H, CH_2OR); 2.39 (d, 1H, *J* = 7.1 Hz, OH); 0.94-0.86 (m, 18H, 2 C(CH_3)$_3$); 0.12-0.02 (m, 12H, 2 Si(CH_3)$_2$); (*syn*-isomer): □9.67 (d, 1H, *J* = 1.0 Hz, CHO); 4.19 (dd, 1H, *J* = 3.8, 1.1 Hz, C**H**CHO); 3.95-3.84 (m, 1H, C**H**OH); 3.80-3.55 (m, 2H, CH_2OR); 2.57 (d, 1H, *J* = 9.3 Hz, OH); 0.94-0.86 (m, 18H, 2 C(CH_3)$_3$); 0.12-0.02 (m, 12H, 2 Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): □201.7, 78.2, 72.8, 62.2, 25.9 (3C), 25.8 (3 C), 18.3 (2C), –3.8, –4.4, –4.8 (2C); (*syn*-isomer): □203.3, 76.7, 73.1, 62.1, 25.9 (3C), 25.8 (3 C), 18.3 (2C), –3.9, –4.4, –4.7, –4.8; HRMS (CI) exact mass calcd for [M–CH_3]$^+$ ($C_{18}H_{39}O_4Si_2$) requires *m*/*z* 375.2387, found *m*/*z* 375.2387. The enantiomeric purity of the corresponding acetonide (after reduction of the title compound with $NaBH_4$ and then acetonide formation with acetone) was determined using a Bodman Chiraldex □-DM (30 m x 0.25 mm) column (110 ºC hold 120 min, ramp 1ºC/min to 150ºC, 23 psi): (2*S*, 3*S*)-enantiomer: t_r = 141.8 min, (2*R*, 3*R*)-enantiomer: t_r = 142.7 min. The diastereomer ratio was determined by ^{1}H NMR analysis of the crude title compound. The optical rotation of the corresponding *anti*-1,3-acetonide was determined, [□]$_D$ = –33.6 (c = 2.7, $CHCl_3$).

(2*S*, 3*S*)-3-Hydroxy-2,3-bis-(*tert*-butyl-diphenyl-silanyloxy)-propionaldehyde (Table 1, entry 5). A suspension of (*tert*-butyl-diphenyl-silanoxy)-actaldehyde (298 mg, 1.0 mmol) and L-proline (11.5 mg, 0.1 mmol) in a mixture of 1,4-dioxane (1.0 mL) and DMF (1.0 mL) was stirred for 48 h at room temperature. The resulting solution was diluted with ethyl acetate (25 mL) and washed successively with water (15 mL) and brine (15 mL). The organic layer was separated, dried

(Na_2SO_4) and then concentrated. Purification of the resulting residue by silica gel chromatography (10:1 pentane: diethyl ether) afforded the title compound as a clear, colorless oil in 61% yield (182 mg, 0.31 mmol), 93% ee (*anti*-diastereomer) and as a mixture of diastereomers (9:1 *anti*:*syn*). IR (film) 3510, 2958, 2932, 2892, 2859, 1734, 1472, 1428, 1113, 823, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : □9.61 (d, 1H, *J* = 1.5 Hz, CHO); 7.70-7.56 (m, 8H, CH_{ar}); 7.48-7.30 (m, 12H, CH_{ar}); 4.23 (dd, 1H, *J* = 3.9, 1.2 Hz, C**H**CHO); 4.08-3.98 (m, 1H, C**H**OH); 3.80 (dd, *J* = 10.2, 6.9 Hz, 1H, CH_2OR); 3.62 (dd, 1H, *J* = 10.2, 6.3 Hz, CH_2OR); 2.13 (d, *J* = 5.4 Hz, 1H, OH); 1.10 (s, 9 H, $C(CH_3)_3$); 1.01 (s, 9H, $C(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) □201.4, 135.7, 135.6, 135.4 (2C), 132.6, 132.5, 132.4 (2C), 130.0 (4C), 129.7 (4C), 127.8 (2C), 127.7 (6C), 79.5, 73.9, 63.2, 19.5, 19.2; HRMS (CI) exact mass calcd for $[M+NH_4]^+$ ($C_{36}H_{48}NO_4Si_2$) requires *m/z* 614.3122, found *m/z* 614.3123; $[□]_D$ = +0.5 (c = 1.1, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis of the crude title compound using a Chiracel ODH and ODH guard column (3.0 % isopropanol/hexanes, 1 mL/min): (2*S*, 3*S*) *anti* isomer t_r = 14.5 min, (2*R*, 3*R*) *anti* isomer t_r = 12.1 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 10.7, 20.0 min. The corresponding 1,3-acetonide-acetal was prepared (as described in Table 1, entry 7) and the *anti*-isomer was isolated by silica gel chromatography (40:1 pentane: diethyl ether) to obtain a optical rotation more suitable for chemical correlation: $[□]_D$ = –6.1 (c = 2.2, $CHCl_3$); HRMS (ESI) exact mass calcd for $[M+Na]^+$ ($C_{39}H_{50}NaO_4Si_2$) requires *m/z* 661.3145, found *m/z* 661.3134.

(2*S*, 3*S*)-3-Hydroxy-2,3-bis-triisopropylsilyloxy-propionaldehyde (Table 1, entry 6). A suspension of trisisopropylsilyloxyacetaldehyde (224 mg, 1.0 mmol) and L-proline (11.7 mg, 0.1 mmol) in DMF (6.7 mL) was stirred for 24 h at room temperature. The resulting solution was diluted with ethyl acetate (25 mL) and washed successively with water (15 mL) and brine (15 mL). The organic layer was separated, dried (Na_2SO_4) and then concentrated. Purification of the resulting residue by silica gel chromatography (40:1 pentane : diethyl ether) afforded the title compound as a clear, colorless oil in 75% yield (169 mg, 0.39 mmol), 95% ee (*anti*-diastereomer) and as a mixture of diastereomers (4:1 *anti*:*syn*). IR (film) 3483, 2945, 2892, 2868, 1734, 1464, 1385, 1117, 1069, 883, 683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □9.68 (d, 1H, *J* = 2.1 Hz, CHO); 4.25 (dd, 1H, *J* = 3.9, 2.1 Hz, C**H**CHO); 4.10-3.94 (m, 1H, C**H**OH); 3.84 (dd, 1H, *J* = 9.9, 6.6 Hz, CH_2OR); 3.79 (dd, 1H, *J* = 9.6, 6.3 Hz, CH_2OR); 2.40 (d, 1H, *J* = 5.4 Hz, OH); 1.16-1.00 (m, 42H,

6 $CH(CH_3)_2$); (*syn*-isomer): □ 9.74 (d, 1H, *J* = 1.5 Hz, CHO); 4.28 (dd, 1H, *J* = 4.9, 1.5 Hz, C**H**CHO); 3.97 (dd, 1H, *J* = 9.9, 2.7 Hz, CH_2OR); 3.89 (m, 1H, C**H**OH); 3.77 (dd, 1H, *J* = 9.9, 4.5 Hz, CH_2OR); 2.73 (d, 1H, *J* = 9.9 Hz, OH); 1.16-1.00 (m, 42H, 6 $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 202.1, 78.9, 74.3, 62.7, 18.0 (12C), 12.4 (3C), 11.9 (3C); (*syn*-isomer): □ 203.8, 74.4, 62.2, 18.0 (12C), 12.3 (3C), 11.9 (3C), one signal obscured by solvent; HRMS (CI) exact mass calcd for $[M+H]^+$ ($C_{22}H_{49}O_4Si_2$) requires *m/z* 433.3169, found *m/z* 433.3176; $[□]_D$ = –3.6 (c = 4.0, $CHCl_3$). The diastereomer ratio was determined by ^1H NMR of the crude product. The enantiomeric purity of the *anti*-diastereomer was determined after conversion of the isolated *anti*-isomer to the 1-hydroxy-3-*p*-nitrobenzoate-derivative as follows: To a solution of the title compound (40 mg, 0.09 mmol) in dichloromethane (0.6 mL), *p*-nitro-benzoylchloride (42.9 mg, 0.23 mmol), 4-dimethylaminopyridine (2.8 mg, 0.02 mmol) and triethylamine (0.06 mL, 0.46 mmol) were added at +4ºC. The resulting mixture was stirred at +4ºC for 3.5 h, before methanol (0.6 mL) and $NaBH_4$ (0.04g, 0.94 mmol) were added, which led to a vigorous gas evolution. After an additional 35 minutes, the mixture was warmed to room temperature and diluted with 5 mL dichloromethane. The resulting solution was washed with saturated $NaHCO_3$ solution, passed through a plug of silica and concentrated. HRMS (ESI) exact mass calcd for $[M+Na]^+$ ($C_{29}H_{53}NNaO_7Si_2$) requires *m/z* 606.3258, found *m/z* 606.3253. The product ratios were determined by HPLC using a Chiracel ODH and ODH guard column (0.16 % isopropanol/hexanes, 1 mL/min): (2*S*, 3*S*) enantiomer t_r = 46.5 min, (2*R*, 3*R*) enantiomer t_r = 41.4 min.

Triisopropylsilyloxy-acetaldehyde. A solution of (Z)-1,4-bis-triisopopylsilyloxy-but-2-ene (6.70 g, 16.7 mmol) and triethylamine (3.5 mL, 25.2 mmol) in dichloromethane/methanol (100 mL/10 mL) was cooled to –78ºC. Ozone was bubbled through the solution until a pale blue color developed. At this time triphenylphosphine (5.70 g, 21.7 mmol) was added and the resulting mixture was stirred for 3 h allowing it to reach 0ºC. After concentration, the residue was treated with pentane (30 mL) causing precipitation of triphenylphosphine oxide. The resulting suspension was poured directly onto a wet column of silica gel (20:1 pentane:diethyl ether). Purification using silica gel (20:1 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 86% yield (6.2 g, 28.6 mmol). IR (film) 2945, 2893, 2868, 1741, 1464, 1133, 883, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.73 (bs, 1H, CHO); 4.26 (d, *J* = 1.1 Hz, 2H, CH_2OR); 1.20-1.02 (m, 21H, 3

$CH(CH_3)_2$); ^{13}C NMR (*7*5 MHz, $CDCl_3$) □ 203.0, 69.7, 18.1 (6C), 12.1 (3C); HRMS (CI) exact mass calcd for $[M+H]^+$ ($C_{11}H_{25}O_2Si$) requires *m/z* 217.1624, found *m/z* 217.1615.

Determination of the absolute stereochemistry of the silyloxy-acetaldehyde-dimers

Each dimer was converted to its corresponding 1,3-acetonide acetal as described above for Table 1, entry 7. Where necessary the *anti* and *syn* isomers were separated (TBS, TBDPS) using silica gel chromatography. The *anti*-isomer was then subjected to protecting group removal to furnish (4*S*, 5*R*)-4-hydroxymethyl-2,2-dimethyl-[1,3]dioxane-5-ol. For all cases this compound was purified by silica gel chromatography and compared to an authentic sample prepared from □-D-glucose by the literature procedure. HRMS (CI) exact mass calcd for $[M+H]^+$ ($C_7H_{15}O_4$) requires *m/z* 163.0970, found *m/z* 163.0976). In all cases (TBS, TBDPS, TIPS), the ^1H- and ^{13}C-NMR-spectra were identical to the natural sample and the specific optical rotation was identical in sign and magnitude to the natural sample: $[□]_D = –28.4$ (c = 0.2, $CHCl_3$); TBS: $[□]_D = –22.4$ (c = 1.2, $CHCl_3$); TBDPS: $[□]_D = –25.4$ (c = 0.4, $CHCl_3$); TIPS: $[□]_D = –26.3$ (c = 1.0, $CHCl_3$).

(2*S*, 3*R*)-4-Triisopropyl-silanyloxy-3-hydroxy-2-methylbutanal (Table 2, entry 1). A solution of freshly distilled propionaldehyde (263 *μ*L, 3.64 mmol) in 0.73 mL DMF pre-cooled to 4 ºC was added slowly over the course of 12 h to a stirring suspension of triisopropylsilanoxy-acetaldehyde (158 mg, 0.73 mmol), L-proline (8.2 mg, 0.073 mmol) and 0.73 mL DMF at 4 ºC. After 18 h, the resulting solution was diluted with diethyl ether (25 mL) and washed successively with water (15 mL) and brine (15 mL). The combined aqueous layers were re-extracted with 3 portions of dichloromethane (15 mL). The organic layers were then combined, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by silica gel chromatography (9:1 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 75% yield (150 mg, 0.55 mmol), 99% ee and as a mixture of diastereomers (4:1 *anti*:*syn*). IR (film) 3435, 2943, 2867, 1725, 1463, 1384, 1107, 996.0, 882.2, 778.5, 682.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.82 (d, *J* = 2.1 Hz, 1H, C**H**O); 3.90-3.65 (m, 3H, C**H**OH, C$\mathbf{H_2}$CHOH); 2.87 (d, 1H, *J* = 4.8 Hz, O**H**); 2.51 (m, 1H, C**H**CH_3); 1.18-0.95 (m, 24H, SiC**H**($C\mathbf{H_3}$)$_2$, CHC$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 204.4, 73.0, 65.2, 49.0, 18.1,

12.1, 10.3; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{14}H_{31}O_3Si$) requires *m/z* 275.2043, found *m/z* 275.2041; $[\alpha]_D$ = + 8.46 (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC analysis of the corresponding bis-*p*-nitrobenzoate ester (obtained by reduction to the corresponding diol with $NaBH_4$ and then treatment with with *p*-nitrobenzoyl chloride), using a Chiracel ODH and ODH guard column (2% isopropanol/hexanes, 1 mL/min) column; (2*R*, 3*S*) *anti* isomer t_r = 33.0 min, (2*S*, 3*R*) *anti* isomer t_r = 35.4 min, (2*R*, 3*R*) and (2*S*, 3*S*) *syn* isomers t_r = 41.0, 44.9 min.

(2*S*, 3*R*)-4-*tert*-Butyldiphenyl-silanyloxy-3-hydroxy-2-methylbutanal (Table 2, entry 2). A solution of freshly distilled propionaldehyde (361 μL, 5.0 mmol) in 1.0 mL dioxane pre-cooled to 4 ºC was added slowly over the course of 24 h to a stirring suspension of *tert*-butyl-diphenylsilanyloxyacetaldehyde (298 mg, 1.0 mmol), L-proline (11.5 mg, 0.10 mmol) and 1.0 mL dioxane at 4 ºC. After 25 h, the resulting solution was diluted with diethyl ether (25 mL) and washed successively with water (15 mL) and brine (15 mL). The combined aqueous layers were then re-extracted with 3 portions of dichloromethane (15 mL). The organic layers were then combined, dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the resulting residue by silica gel chromatography (9:1 hexanes:ethyl acetate) afforded the title compound as a clear, colorless oil in 84% yield (300 mg, 0.84 mmol), 99% ee and as a mixture of diastereomers (5:1 *anti*:*syn*). IR (film) 3434, 3050, 2929, 2856, 1725, 1590, 1462, 1428, 1113, 996.6, 823.4, 740.3, 702.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (d, *J* = 2.4 Hz, 1H, C**H**O); 7.65 (m, 4H, Ar-H); 7.42 (m, 6H, Ar-H); 3.88 (m, 1H, C**H**OH); 3.76 (dd, 1H, *J* = 10.0, 3.7 Hz, C$\mathbf{H_2}$CHOH); 3.65 (dd, 1H, *J* = 10.0, 6.0 Hz, C$\mathbf{H_2}$CHOH); 2.69 (d, 1H, *J* = 4.8 Hz, O**H**); 2.58 (m, 1H, C**H**CH_3); 1.06 (m, 12H, Si(C$\mathbf{H_3}$)$_3$, CHC$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 135.7, 132.9, 130.2, 128.0, 73.2, 49.0, 27.2, 19.6; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{21}H_{29}O_3Si$) requires *m/z* 357.1886, found *m/z* 357.1870; $[\alpha]_D$ = + 8.78 (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel ODH and ODH guard column (2% ethanol/hexanes, 1 mL/min) column; (2*R*, 3*S*) *anti* isomer t_r = 26.2 min, (2*S*, 3*R*) *anti* isomer t_r = 31.5 min, (2*R*, 3*R*) and (2*S*, 3*S*) *syn* isomers t_r = 35.4, 41.5 min.

(2*S*, 3*R*)-4-Triisopropylsilanoxy-3-hydroxy-2-isopropylbutanal (Table 2, entry 3). A solution of freshly distilled isovaleraldehyde (354 μL, 3.3 mmol) in 0.66 mL DMF pre-cooled to 4

ºC was added slowly over the course of 12 h to a stirring suspension of triisopropylsilanoxyacetaldehyde (143 mg, 0.66 mmol), L-proline (7.5 mg, 0.066 mmol) and 0.66 mL DMF at 4 ºC. After 18 hours, the resulting solution was diluted with diethyl ether (25 mL) and washed successively with water (15 mL) and brine (15 mL). The combined aqueous layers were then re-extracted with 3 portions of dichloromethane (15 mL). The organic layers were then combined, dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the resulting residue by silica gel chromatography (9:1 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 54% yield (107 mg, 0.36 mmol), 99% ee and as a mixture of diastereomers (4:1 *anti* : *syn*). IR (film) 3480, 2960, 2868, 1722, 1464, 1388, 1115, 1013, 996.4, 882.5, 795.1, 682.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.80 (d, 1H, *J* = 3.9 Hz, C**H**O); 4.03 (m, 1H, C**H**OH); 3.73 (dd, 1H, *J* = 10.2, 4.2 Hz, C**H**$_2$OSi); 3.62 (dd, 1H, *J* = 10.2, 6.9 Hz, C**H**$_2$OSi); 2.71 (d, 1H, *J* = 5.1 Hz, CHO**H**); 2.24 (m, 1H, C**H**$(CH_3)_2$); 2.05 (ddd (apparent dt), 1H, *J* = 7.8, 3.9, 3.9 Hz, C**H**CHO); 1.17-0.95 (m, 27H, CH(C**H$_3$**)$_2$, SiC**H**(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 206.2, 71.0, 66.2, 60.0, 26.6, 20.9, 20.4, 18.1, 12.0; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{16}H_{35}O_3Si$) requires *m/z* 303.2356, found *m/z* 303.2348. $[□]_D$ = –4.11 (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC analysis of the corresponding bis-*p*-nitrobenzoate ester (obtained by reduction to the corresponding diol with $NaBH_4$ and then treatment with *p*-nitrobenzoyl chloride), using a Chiracel ODH and ODH guard column (2% isopropanol/hexanes, 1 mL/min) column; (2*S*, 3*R*) *anti* isomer t_r = 24.8 min, (2*R*, 3*S*) *anti* isomer t_r = 33.7 min, (2*R*, 3*R*) and (2*S*, 3*S*) *syn* isomers t_r = 27.9, 30.7 min.

(2*S*, 3*R*)-4-Benzyloxy-3-hydroxy-2-isopropylbutanal (Table 2, entry 4). A solution of freshly distilled benzyloxyacetaldehyde (141 μL, 1.0 mmol) in 1.0 mL dimethylformamide pre-cooled to 4 ºC was added slowly over the course of 18 h to a stirring suspension of isovaleraldehyde (214 μL, 2.0 mmol), L-proline (11.5 mg, 0.10 mmol) and 1.0 mL dimethylformamide at 4 ºC. After 19 hours, the resulting solution was diluted with diethyl ether (25 mL) and washed successively with water (15 mL) and brine (15 mL). The combined aqueous layers were then re-extracted with 3 portions of dichloromethane (15 mL). The organic layers were then combined, dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the resulting residue by silica gel chromatography (4:1 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 64% yield (151 mg, 0.64 mmol), 95% ee and as a mixture of diastereomers (4:1 *anti* : *syn*). IR (film) 3456, 2961, 2929,

2871, 1721, 1468, 1453, 1390, 1370, 1101, 1028, 990.3, 946.0, 914.4, 738.2, 698.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 9.81 (d, 1H, *J* = 3.6 Hz, C**H**O); 7.33 (m, 5H, Ar-H); 4.54 (s, 2H, C$\mathbf{H_2}$Ph); 4.18 (m, 1H, C**H**OH); 3.57 (dd, 1H, *J* = 6.6, 3.0 Hz, C$\mathbf{H_2}$OBn); 3.45 (dd, 1H, *J* = 9.3, 6.6 Hz, C$\mathbf{H_2}$OBn); 2.63 (d, 1H, *J* = 5.1 Hz, CHO**H**); 2.23 (m, 1H, C**H**$(CH_3)_2$); 2.07 (ddd (apparent dt), 1H, *J* = 7.8, 3.9, 3.9 Hz, C**H**CHO); 1.06 (d, 3H, *J* = 6.9 Hz, C$\mathbf{H_3}$); 0.95 (d, 3H, *J* = 6.9 Hz, C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) 206.2, 137.7, 128.7, 128.0, 73.8, 73.1, 69.7, 60.4, 26.6, 21.1, 20.6; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{14}H_{21}O_3$) requires *m/z* 237.1491, found *m/z* 237.1492. $[]_D$ = –14.4 (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (4% isopropanol/hexanes, 1 mL/min) column; (2*R*, 3*S*) *anti* isomer t_r = 22.4 min, (2*S*, 3*R*) *anti* isomer t_r = 24.5 min, (2*R*, 3*R*) and (2*S*, 3*S*) *syn* isomers t_r = 29.3, 31.8 min.

(2*S*, 3*S*)-3-Hydroxy-4-methyl-2-triisopropylsilanyloxy-pentanal (Table 2, Entry 5). A solution of freshly distilled triisopropylsilanyloxyacetaldehyde (216 mg, 1.0 mmol) in 1.0 mL dimethylformamide pre-cooled to 4 ºC was added slowly over the course of 36 h to a stirring suspension of isobutyraldehyde (272 L, 3.0 mmol), L-proline (22.6 mg, 0.2 mmol) and 1.0 mL dimethylformamide at 4 ºC. After 37 h, the resulting solution was diluted with diethyl ether (25 mL) and washed successively with water (15 mL) and brine (15 mL). The combined aqueous layers were then re-extracted with 3 portions of dichloromethane (15 mL). The organic layers were then combined, dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the resulting residue by silica gel chromatography (39:1 hexanes:ethyl acetate) afforded the title compound as a clear, colorless oil in 43% yield (124 mg, 0.43 mmol), 99% ee and as a mixture of diastereomers (8:1 *anti*:*syn*). IR (film) 3464, 2947, 2864, 1735, 1464, 1379, 1316, 1254, 1109, 1064, 1016, 958.5, 917.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 9.70 (d, 1H, *J* = 2.1 Hz, CHO); 4.14 (dd (apparent t), 1H, *J* = 3.3 Hz, C**H**CHO); 3.48 (m, 1H, C**H**OH); 2.67 (d, 1H, *J* = 2.1 Hz, CHO**H**); 1.78 (m, 1H, C**H**$(CH_3)_2$); 1.16-1.01 (m, 24H, SiC**H**$(C\mathbf{H_3})_2$, CHC$\mathbf{H_3}$); 0.94 (d, 3H, *J* = 9.0 Hz, CH$\mathbf{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) 203.6, 80.7, 78.9, 29.7, 19.6, 19.2, 18.3, 12.5; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{15}H_{34}O_3Si$) requires *m/z* 289.2198, found *m/z* 289.2201. $[]_D$ = –2.47 (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the corresponding acetonide derived by $NaBH_4$ reduction of the title aldehyde and then ketalization of the resulting diol with 2-methoxypropene (using the method of Lipshutz[3]). GLC analysis was conducted using a Bodman Chiraldex -DM

(30 m x 0.25 mm) column (110 ºC isotherm, 23 psi); (2*S*, 3*S*) *anti* isomer t_r = 88.4 min, (2*R*, 3*R*) *anti* isomer t_r = 90.5 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 100.4, 102.2 min.

Determination of the absolute stereochemistry of (2*S*, 3*S*)-3-Hydroxy-4-methyl-2-triisopropylsilanyloxy-pentanal by correlation to (*2S*, 3*R*)-3-[(4-Methoxyphenyl)methoxy]-4-methyl-1,2-pentanediol. A stirring solution of (2*S*,3*S*)-3-Hydroxy-4-methyl-2-triisopropylsilanyloxy-pentanal (70 mg, 0.24 mmol) in 10.0 mL of 4:1 dichloromethane:ethanol was treated with $NaBH_4$. After stirring for 5 minutes, the reaction was treated with a saturated aqueous solution of $NaHCO_3$, and extracted with 3 portions of dichloromethane (15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and then concentrated *in vacuo*. The resulting residue was then taken up in DMF (250 μL), and then treated with triisopropyl chloride (55 μL, 0.26 mmol) and imidazole (35 mg, 0.52 mmol) according to the method of Cunico.[4] After stirring for 12 hours, the mixture was diluted in ether (10 mL), and then washed successively with saturated aqueous solutions of NH_4Cl (10 mL), and $NaHCO_3$ (10 mL), and water (10 mL). The organics were separated and then concentrated and the resulting residue was then taken up in THF (2 mL), and treated sequentially with NaH (6.7 mg, 0.28 mmol), 4-methoxy-benzyl chloride (38 μL, 0.28 mmol) and tetrabutylammonium iodide (9 mg, 0.024 mmol). After stirring for 14 hours, the mixture was diluted in ether (20 mL), and then washed successively with saturated aqueous solutions of NH_4Cl (10 mL), and $NaHCO_3$ (10 mL), and water (10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. The resulting residue was purified by silica gel (0–2.5% ethyl acetate in hexanes, linear gradient) to afford a 51% yield (63 mg, 0.12 mmol) of (*2S*, 3*R*)-3-[(4-Methoxyphenyl)methoxy]-4-methyl-1,2-triisopropylsilanyloxy-pentane. To this compound was added tetrabutylammonium fluoride (174 μL, 1 M in tetrahydrofuran). After refluxing for 12 hours, the mixture was diluted in ether and washed successively with saturated aqueous solutions of NH_4Cl (10 mL), and $NaHCO_3$ (10 mL), and water (10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (5:1 ethyl hexanes:ethyl acetate) to afford a 33% yield (10 mg, 0.04 mmol) of (*2S*, 3*R*)-3-[(4-Methoxyphenyl)methoxy]-4-methyl-1,2-pentanediol; $[\alpha]_D$ = -11.2 (c = 1.0, $CHCl_3$) (lit. $[\alpha]_D$ = – 14.0 (c = 1.19, $CHCl_3$) for (*2S*, 3*R*)-3-[(4-methoxyphenyl)methoxy]-4-methyl-1,2-pentanediol).[5]

(2*S*, 3*S*)-2-(Benzylyloxy)-3-hydroxy-4-methyl-pentanal (Table 2, entry 6). A solution of benzyloxyacetaldehyde (150.2 mg, 1.0 mmol) in dimethylformamide (1.0 mL) was added slowly over the course of 24 hours to a suspension of isobutryldehyde (914 μL, 10.0 mmol) and L-proline (23.0 mg, 0.20 mmol) in DMF (1.0 mL) at room temperature. The resulting solution was diltued with water, extracted with ethyl acetate and washed with brine and then dried over anhydrous Na_2SO_4. The organics were then concentrated and the resulting residue was purified by silica gel chromatographt (1:3 ethyl acetate: hexanes) to afford the title compound as a clear, colorless oil in 33% yield (74 mg, 0.33 mmol), 96% ee (*anti*), and as a mixture of diastereomers (7:1 *anti*:*syn*). IR (film) 3460, 3032, 2963, 2932, 2874, 1732, 1497, 1455, 1101, 1027, 738.5, 698.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.78 (d, 1H, J = 2.7 Hz, CHO); 7.36 (m, 5H, Ar-H); 4.72 (d, 1H, J = 12.0 Hz, CH_2Ar); 4.56 (d, 1H, J = 12.0 Hz, CH_2Ar); 3.81 (dd, 1H, J = 4.8, 2.4 Hz, C**H**CHO); 3.69 (m, 1H, C**H**OH); 2.28 (d, 1H, J = 4.5 Hz, OH); 1.92 (m, 1H, C**H**$(CH_3)_2$); 0.95 (d, 3H, J = 6.9 Hz, CH_3); 0.95 (d, 3H, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6, 137.1, 128.9, 128.6, 128.4, 84.3, 73.2, 29.8, 19.4, 17.7; $[\alpha]_D$ = –53.1 (c = 0.47, $CHCl_3$). The enantiomeric purity of the corresponding diol (by treatment with $NaBH_4$) was determined by HPLC analysis using a Chiracel AD and AD guard column (5% ethanol/hexanes, 1 mL/min): (2*S*, 3*S*)-enantiomer: t_r = 14.7 min, (2*R*, 3*R*)-enantiomer: t_r = 17.3 min, *syn* isomers t_r = 24.7, 27.4 min. The diastereomer ratio was determined by ^1H NMR analysis of the crude title compound and verified by HPLC analysis after $NaBH_4$ reduction.

---

[1] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.
[2] W. C. Still, M. Kahn, M, A. J. Mitra, *J. Org. Chem.* **1978,** *43*, 2923.
[3] B. H. Lipshutz, J. C. Barton, *J. Org. Chem.* **1988**, *53*, 4495.
[4] R. F. Cunico, L. Bedell, *J. Org. Chem.* **1980**, *45*, 4797.
[5] M. Oikawa, T. Ueno, H. Oikawa, A. Ichihara, *J. Org. Chem.* **1995**, *60*, 5048.